REMARKS

Reconsideration is respectfully requested. Claims 7, 8, 10, 25, 26, 28, 31, 44, 45, 46, 49, 50, 51, 52 and 53 are pending. Claims 1-6, 9, 11-24, 27, 29-30, 32-43 and 47-48 are canceled. Claims 7, 8, 25, 26 and 44 are amended. Claims 45, 46 and 49-52 are withdrawn. New claim 53 has been added. No new matter has been added due to the amendments. Amendments to and cancellation of the claims do not affect inventorship.

Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Claim Amendment

Claims 7, 8, 25, 26 and 44 are amended. Support for the amendments to claims 7 and 25 can be found, for example, in paragraph [0097] of the Specification. Support for the amendments to claims 8 and 26 can be found, for example, in paragraph [0118] of the Specification. Claim 44 is amended for technical clarity. Support can be found, for example, in paragraph [0211] of the Specification.

Objection to the Specification

The Examiner has objected to the Specification and amendments made therein. Applicants respectfully traverse as follows:

The Examiner has objected to the Specification as being inconsistent as identifying the amino acid sequence of the atomic coordinate listing of FIG. 3 as SEQ ID NO:5. The Examiner states "[a]ccording to Figure 3, the first amino acid in the listing is Gly. However, the paper copy of the sequence listing identifies Met as the first amino acid of SEQ ID NO:5." As set forth in the legend, the amino acids of FIG. 3 are indicated by atom number (A) as well as amino acid number (E). Atom 1 in FIG. 3 (see column A) is derived from amino acid 12 (see column E), which is glycine (GLY). As is evident from SEQ ID NO: 5, glycine is the 12th amino acid in the sequence. Therefore, FIG. 3 accurately represents the atomic coordinate listing of the amino acid sequence set forth in SEQ ID NO: 5. Thus, the Examiner is respectfully requested to withdrawn the instant objection.

The Examiner has also objected to the Specification because the Examiner contends that the amendment filed on 3/5/07 introduces new matter in contravention of 35 U.S.C. § 132(a). The Examiner's attention is again directed to FIG. 3 which clearly sets forth the first amino acid for which structure coordinates are reported as amino acid no. 12. Therefore, it stands to reason that structure coordinates for residues 1-11 were not reported. Applicant's amendment to paragraph [0120] on 3/5/07 was simply the correction of a typographical error, and the amendment was fully supported by the drawings (which form part of the disclosure) filed along with the original application.

Claim Rejection - 35 U.S.C. § 112, Second Paragraph

Claims 8, 26 and 46 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully respond as follows:

Claim 46 has been withdrawn thereby rendering the rejection moor with respective to this claim. Without acquiescing to the propriety of the rejection, claims 8 and 26 have been amended to clarify the scope of the invention. Support for the amendment is present at [0118] of the Specification.

Claim Rejection - 35 U.S.C. § 112, First Paragraph

Claims 8, 10, 26, 28 and 46 stand rejected under 35 U.S.C. § 112, first paragraph, as containing new matter. Claims 7, 8, 10, 25, 26, 28, 31, 44, 45-46, and 49-52 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description and enablement requirement. Applicants respectfully traverse as follows:

The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of

the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983)). **The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement.** *See* M.P.E.P. § 2163.02 (emphasis added).

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498,

I. New Matter

Claims 8, 26, 46 are rejected as containing new matter because of the recitation of "trimer." Claim 46 has been withdrawn thereby rendering the rejection moor with respective to this claim. Without acquiescing to the propriety of the rejection, Applicants note that claims 8 and 26 have been amended to clarify the scope of the invention. Support for the amendment is present at [0118] of the Specification, which recites that the asymmetric unit cell comprises three protein molecules in a complex.

Claims 10 and 28 are rejected as containing new matter because the original claims fail to provide support for the limitation "resolution of a value equal to or less than 3.0 Angstroms." Applicants respectfully respond as follows:

Paragraphs [0147] and [0192] of the Specification as originally filed, provide support for the above limitation. Paragraph [0147] states that "the root mean square deviation of alpha-carbon atoms or non-hydrogen atoms may optionally be less than 2.7 Å, 2.5 Å, 2.0 Å, 1.5 Å, 1 Å, 0.5 Å, or less," and paragraph [0192] states that the structure coordinates of the protein complexes may be refined versus 1.5-3Å resolution X-ray data.

II. Written Description and Enablement

Claims 7, 8, 10, 25, 26, 28, 31, 44, 45-46, and 49-52 stand rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description and enablement requirement.

Claims 45-46 and 49-52 have been withdrawn, rendering the rejections moot with respect to these claims.

Without acquiescing to the propriety of the rejection, Applicants have amended claims 7, 8, 25 and 26 in order to clarify the scope of the claims. Therefore, Applicants request that the written description and enablement rejections with respect to claims 7, 8, 10, 25, 26, 28 and 31 be withdrawn.

Claim 44 has been amended to recite a "non-crystalline" protein consisting of SEQ ID NO:5. Support for this amendment can be found at paragraph [0211] of the specification as filed. Therefore, Applicants request that the written description rejection with respect to claim 44 be withdrawn.

Claim Rejection - 35 U.S.C. § 102

Claim 44 stands rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pat. No. 7,169,801 to Bressi et al. Applicants respectfully traverse.

For an anticipation rejection under 35 U.S.C. § 102 to be proper, a single reference must disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); M.P.E.P. § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claim 44, as amended, recites "A non-crystalline protein consisting of SEQ ID NO:5." The specification discloses that SEQ ID NO:5 has 405 amino acids, and is generated by limited proteolysis of the full length HDCA-2 (residues 1-448 of SEQ ID NO:1) protein fused with 6-histidine tag at the C-terminus. See paragraph [0211].

Bressi discloses a full-length HDAC-2 polypeptide having an additional tripeptide "MGS" at the N-terminus (see SEQ ID NO:3) relative to the native HDAC-2 sequence. Cleavage of the polypeptide set forth in Bressi's SEQ ID NO:3 with trypsin would always yield a partial polypeptide having the additional "MGS" tripeptide at the N-terminus. Claim 44 is directed to a non-crystalline protein consisting of SEQ ID NO:5, which does not contain the additional "MGS" tripeptide at the N-terminus, and thus is novel and non-obvious over the polypeptides set forth in Bressi. Because the Bressi reference does not teach each and every limitation of claim 44, it cannot anticipate claim 44. As such, Applicants respectfully request withdrawal of the instant rejection.

Claim Rejection - 35 U.S.C. § 101

Claim 44 stands rejected under 35 U.S.C. § 101 on the basis that the claimed the invention is directed to non-statutory subject matter.

Claim 44, as amended, is directed to "A non-crystalline protein consisting of SEQ ID NO:5." SEQ ID NO:5 is derived by cleavage of SEQ ID NO:1 with TPCK-Trypsin (obtained from Pierce- see [0211] of Specification), in which the trypsin is treated with L-1-tosylamido-2-phenylethyl chloromethyl ketone (TPCK) to inhibit contaminating chymotrypsin activity without affecting trypsin activity. See attached description from Pierce's web site. Since TPCK-Trypsin is a modified form of trypsin that is different from the naturally occurring form of trypsin, the latter being typically contaminated with chymotrypsin, there is nothing to suggest that cleavage of SEQ ID NO:1 with the trypsin mixture found in the digestive system would yield the exact polypeptide denoted by SEQ ID NO:5. Thus, the "hand of man" is clearly implicated in the generation of SEQ ID NO:5. Therefore, Applicants respectfully request withdrawal of the instant rejection.

Claim Rejection- Double Patenting

Claims 45 and 46 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of co-pending Application No. 10/826,134. Since claims 45 and 46 are withdrawn from the instant application, the rejection is rendered moot. Applicants therefore request withdrawal of the instant rejection.

Serial No.: 10/826,170
Filing Date: 04/16/2004

CONCLUSION

In view of the foregoing amendments and arguments, it is believed that all claims now pending in this application are in condition for allowance. Should the Examiner not agree, the Applicant respectfully asks the Examiner to contact the undersigned at the phone number below to discuss any remaining issues and accelerate the examination and allowance of this application. Authorization is granted to charge any outstanding fees due at this time for the continued prosecution of this matter to Morgan, Lewis & Bockius LLP Deposit Account No. 50-0310 (Client Matter No. 067450-5013US).

Respectfully submitted,

Dated: 9/3/07

By: _____

Lekha Gopalakrishnan, Reg. No. 46,733
Tel. No. (214) 466-4116

Filed Under 37 C.F.R. § 1.34

On behalf of:
Robin M. Silva, Reg. No. 38,304

Customer Number: 67374
Morgan, Lewis & Bockius LLP
One Market, Spear Street Tower
San Francisco, CA 94105
Telephone: (415) 442-1000
Facsimile: (415) 442-1001

DOCUMENT CENTER

> Certificate of Analysis
> Instruction Books
> MSDS
> Print This Page
> Email This Page
> Request A Catalog

USER PROFILE

Email Address:

Password:

▶ LOG IN

> I Forgot My Password

> New User Registration
> Why Register?

SHOPPING CART

> Ordering Information
▶ Shipping Info
▶ Credit Info
▶ Returns Info

> Current Order
▶ Currently Empty
▶ Order Form

TPCK Trypsin and Immobilized TPCK Trypsin

Use Trypsin as an ideal protease to make reproducible peptide fragments for protein analysi

Trypsin is a 23.8 kDa pancreatic serine endoprotease derived from trypsinogen, an inactive pre zymogen, after enzymatic removal of an n-terminal leader sequence by enterokinase. Once sor trypsin has been formed it can catalyze the conversion of more trypsinogen into its catalytically- form. Trypsin is treated with L-1-tosylamido-2-phenylethyl chloromethyl ketone (TPCK) to inhibit contaminating chymotrypsin activity without affecting trypsin activity.

Trypsin has a wide range of applications including amino acid analysis and protein sequencing, mapping and structural studies. Enzymes such as trypsin and chymotrypsin have become impo tools in sequencing studies since they are highly selective in their cleavage of peptide bonds. T cleaves only those peptide bonds in which the carboxyl group is contributed by a lysine or an ar residue, regardless of the length or amino acid sequence of the chain.

Immobilized trypsin can be substituted for free trypsin in any application, and is advantageous because it virtually eliminates autolysis, eliminates contamination of a sample with the protease allows control of the digestion by removing the trypsin. Immobilized trypsin is also more stable a heat-induced denaturation, resulting in longer maintenance of activity.

Trypsin applications

- Removal of adherent cells from tissue culture flasks
- Preparing tryptic fragments for Edman degradation sequencing
- Immobilized trypsin can be used to purify soybean trypsin inhibitor

Properties of Trypsin

Specificity	Cleaves specifically at the carboxyl side of arginine and lysine residues
Source	Bovine pancreas
Molecular weight	23,800
Protease type	Serine protease
Uses/applications	Specific protein fragmentation for protein identification and sequence analys
Reaction conditions	pH 7.5-9.0, 37°C
Storage conditions	Store at 4°C
Inhibitors	TLCK, DFP, Aprotinin, PMSF
Unit definition	One unit is equal to 1 µmole of TAME (*p* -toluenesulfonyl-L-arginine methyl in the presence of Ca^{2+} hydrolyzed/minute at pH 8.2, 25°C. (One TAME uni 57.5 National Formulatory Units).

Related products

In-Gel Tryptic Digestion Kit

In-Solution Tryptic Digestion and Guanidation Kit

Other proteases

Protease selection chart

References

- Cunningham, L.W. (1954) Molecular-kinetic properties of crystalline diisopropyl phosphor trypsin. *J. Biol. Chem.* **211,** 13.
- Walsh, K.A. and Neurath, H. (1964) Trypsinogen and chymotrypsinogen as homologous proteins. *Proc.Natl. Acad Sci. USA,* **52,** 884.
- Kostka, V. and Carpenter, F.H. (1964) Inhibition of chymotrypsin activity in crystalline tryp preparations. *J. Biol. Chem.* **239,** 1799-1803.
- Walsh, K.A. "Trypsinogens and trypsins of various species" in *Methods of Enzymology,* V XIX, (Perlman, G. E; and Lorand, L; eds) pp. 41.
- Woolhead , C.A., *et al.* (2001) *J. Biol. Chem.* **276,** 14607-14613.
- Rush, J., *et al.* (2005) Nature Biotech. **23,** 94-101.

*** Trypsin, Immobilized Trypsin and other proteases are available in bulk quantities for manufacturing applications.**

Ordering Information Certificate of Analysis Instruction Book with Protocols

Buy	Product #	Description		Pkg. Size	Files	F
Add	20230	Immobilized Trypsin, TPCK Treated		2 ml		
		Specific activity:	>200 TAME units/ml gel			
		Support:	Crosslinked 4% beaded agarose			
		Form:	Slurry in 50% glycerol, 0.05% NaN_3			
Add	20233	TPCK Trypsin		50 mg		
		Specific activity:	> 10,350 BAEE units/mg protein			
			> 180 TAME units/mg protein			
			> 3,450 USP/NF units/mg protein			
		Purity:	less than 0.02% chymotrypsin			